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RESEARCH ARTICLE | *Higher Neural Functions and Behavior*

Modulation of auditory gamma-band responses using transcranial electrical stimulation

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Jones KT, Johnson EL, Tauxe ZS, Rojas DC. Modulation of auditory gamma-band responses using transcranial electrical stimulation. *J Neurophysiol* 123: 2504–2514, 2020. First published June 3, 2020; doi:10.1152/jn.00003.2020.—Auditory gamma-band (>30 Hz) activity is a biomarker of cortical excitation/inhibition (E/I) balance in autism, schizophrenia, and bipolar disorder. We provide a comprehensive account of the effects of transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) on gamma responses. Forty-five healthy young adults listened to 40-Hz auditory click trains while electroencephalography (EEG) data were collected to measure stimulus-related gamma activity immediately before and after 10 min of 1 mA tACS (40 Hz), tDCS, or sham stimulation to left auditory cortex. tACS, but not tDCS, increased gamma power and phase locking to the auditory stimulus. However, both tACS and tDCS strengthened the gamma phase connectome, and effects persisted beyond the stimulus. Finally, tDCS strengthened the coupling of gamma activity to alpha oscillations after termination of the stimulus. No effects were observed in prestimulus gamma power, the gamma amplitude connectome, or any band-limited alpha measure. Whereas both stimulation techniques synchronize gamma responses between regions, tACS also tunes the magnitude and timing of gamma responses to the stimulus. Results reveal dissociable neurophysiological changes following tACS and tDCS and demonstrate that clinical biomarkers can be altered with noninvasive neurostimulation, especially frequency-tuned tACS.

NEW & NOTEWORTHY Gamma frequency-tuned transcranial alternating current stimulation (tACS) adjusts the magnitude and timing of auditory gamma responses, as compared with both sham stimulation and transcranial direct current stimulation (tDCS). However, both tACS and tDCS strengthen the gamma phase connectome, which is disrupted in numerous neurological and psychiatric disorders. These findings reveal dissociable neurophysiological changes following two noninvasive neurostimulation techniques commonly applied in clinical and research settings.

biomarker; connectome; cross-frequency coupling; gamma; tACS; tDCS

INTRODUCTION

Neurological and clinical disorders coincide with dysfunction in oscillatory metrics and connectivity that serve as biomarkers for disease (Voytek and Knight 2015). For example, in autism spectrum disorder (ASD), language dysfunctions observed during development (reviewed in Mody and Belliveau 2013) also manifest with underlying disruptions in connectivity within language networks (Dinstein et al. 2011). Given the limited success of behavioral interventions (Dawson et al. 2010; Rogers et al. 2012; Van Hecke et al. 2015) and drug treatments (Erickson et al. 2014), it is critical to identify biomarkers of ASD and other disorders that can be targeted to develop treatments that need not rely solely on behavioral or drug interventions (reviewed in Port et al. 2014, 2015).

Abnormal auditory poststimulus gamma (>30 Hz) activity in the superior temporal gyrus, which contains the auditory cortex, is a biomarker of ASD (Gandal et al. 2010; Grice et al. 2001; Rojas et al. 2008; Rojas and Wilson 2014; Sun et al. 2012; Wilson et al. 2007), as well as schizophrenia (Edgar et al. 2014; Krishnan et al. 2009; Steinmann et al. 2014a) and bipolar disorder (Maharajh et al. 2007). Gamma activity is believed to reflect coordinated interactions between excitatory neurons and inhibitory interneurons (E/I balance), as measured in local field potentials (reviewed in Buzsáki and Wang 2012). Importantly, gamma activity can be measured noninvasively using electroencephalography (EEG), and evidence from EEG corroborates abnormal auditory gamma responses as a reliable biomarker of ASD symptomology. For instance, auditory poststimulus evoked gamma power (EP) and functional connectivity are reduced in ASD compared with neurotypical individuals (Edgar et al. 2015, 2016; Gandal et al. 2010; Rojas et al. 2008; Wilson et al. 2007). Indeed, reduced auditory poststimulus gamma EP is observed in adults with ASD, adult first-degree relatives (Rojas et al. 2008, 2011), and children at high-risk of developing ASD (e.g., siblings of children with ASD; Elsabbagh et al. 2009; Tierney et al. 2012). A longitudinal study revealed that clinical ASD severity was predicted by reductions in auditory poststimulus gamma EP (Port et al. 2016). Furthermore, the coupling of gamma activity to alpha (~10 Hz) oscillations—i.e., cross-frequency phase-amplitude coupling (PAC), the purported code for information transfer across temporal scales (Canolty and Knight 2010)—is reduced in ASD in the fusiform face area during face viewing (Khan et al. 2013).

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One way to target cortical E/I balance is through transcranial electrical stimulation, such as transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS). These techniques offer practical translational potential because they are noninvasive, safe (Matsumoto and Ugawa 2017; Nitsche et al. 2003), and well tolerated (Kessler et al. 2012). Because of its frequency specificity, tACS holds promise for directly targeting rhythmic activity within the typical EEG range (Kutchko and Fröhlich 2013). Indeed, 1–2 mA of tACS modulates cortical activity through entrainment of neural oscillations to the stimulated frequency (reviewed in Herrmann et al. 2013), suggesting that gamma tACS could target gamma activity in auditory cortex (Preisig et al. 2020; Rufener et al. 2016, 2019; Wöstmann et al. 2018). A recent study reported that tACS also increases functional connectivity to the stimulated region (Kar et al. 2020). In contrast, 1–2 mA of tDCS modulates the excitability of underlying neural populations (Antal et al. 2004; Nitsche and Paulus 2000; Paulus 2011; Rosenkranz et al. 2000; Stagg and Nitsche 2011). In addition to modulating human auditory processing (Heimrath et al. 2016), tDCS has been shown to treat depression (Brunoni et al. 2011; Fregni et al. 2006), reduce episodic memory deficits in Alzheimer's (Ferrucci et al. 2008) and Parkinson's diseases (Boggio et al. 2006), ameliorate aphasia (Baker et al. 2010; Fridriksson et al. 2011; Monti et al. 2008), and improve poststroke motor function (Fregni et al. 2005; Kim et al. 2009; Suzuki et al. 2012). In ASD, tDCS has been shown to improve social performance in children, with effects lasting up to two months (Wilson et al. 2017), and to improve working memory (van Steenburgh et al. 2017). However, conflicting reports exist, as some tDCS studies report a reduction in ASD symptom severity on standardized tests (Amatachaya et al. 2014; Gómez et al. 2017) whereas others do not (Nobusako et al. 2017). These conflicting findings illuminate the need to understand how different neurostimulation techniques might modulate biomarkers of disordered behavior. Establishing the efficacy of noninvasive neurostimulation in targeting clinical biomarkers is critical to the development of future individually tailored treatment regimens.

The goal of the present study is to provide a systematic investigation of the effects of gamma tACS and tDCS on auditory gamma responses. Participants received 10 min of 1 mA tACS (40 Hz), tDCS, or sham stimulation to left auditory cortex. Immediately before and after stimulation, participants listened to 40-Hz auditory click trains while EEG data were collected to measure stimulus-related gamma activity (Fig. 1*A*). This auditory task reliably elicits gamma responses in frontocentral channels and bilateral temporal lobes, as measured by EEG (McFadden et al. 2014) and magnetoencephalography (MEG; Legget et al. 2017), and consistent with decades of literature showing auditory-evoked potentials (AEP) in the same regions (Davis et al. 1966; Picton et al. 1999). We hypothesized that gamma tACS would increase auditory gamma responses compared with sham stimulation. We additionally tested the effects of tDCS on gamma responses, as well as the effects of both tACS and tDCS on the gamma functional connectome and alpha-gamma PAC, to delineate how different neurostimulation techniques might affect various EEG metrics associated with disordered behavior. Last, we confirmed the specificity of auditory gamma responses against the induced alpha oscillation (Jensen and Mazaheri 2010), which may play a role in auditory attention (Wöstmann et al. 2016).

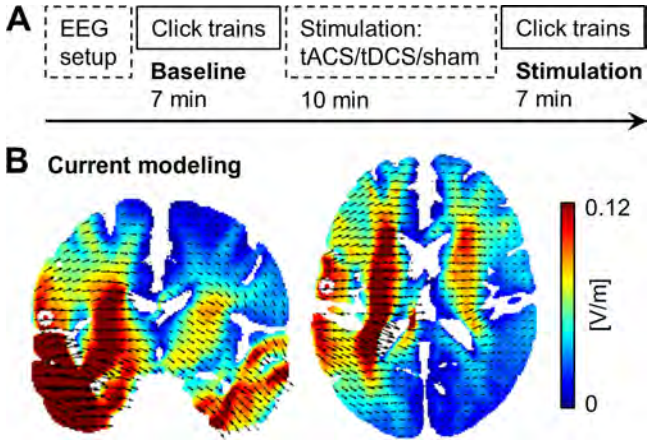

Fig. 1. Study design and neurostimulation. *A*: study design. Participants performed the auditory task while electroencephalogram (EEG) data were recorded immediately before and after 10 min of transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS), or sham stimulation. *B*: electrical field changes following neurostimulation. We applied 1 mA tACS, tDCS, or sham stimulation with the anode positioned at T7 and the cathode at the contralateral cheek.

MATERIALS AND METHODS

Participants. Forty-five right-handed Colorado State University undergraduates took part in the study (mean ± SD age: 20.9 ± 2.3 yr; 19 men). Participants were randomly assigned to one of three neurostimulation groups: tACS, tDCS, or sham stimulation. All participants were screened for use of neuroleptic, hypnotic, and seizure medications, and reported no history of neurological disorders or brain injury. The Colorado State University Institutional Review Board approved the study protocols and all participants gave written informed consent before participation.

Electroencephalography. EEG data were recorded in using a g.tec head cap (Guger Technologies GmbH, Schiedlberg, Austria) at a sampling rate of 512 Hz from 14 channels (F3, C3, P3, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz, F4, C4, P4; International 10–20 System), referenced to the right mastoid. This channel montage captures the known frontocentral distribution of the auditory response (Davis et al. 1966; McFadden et al. 2014; Picton et al. 1999). Channels were connected to a g.tec USBamp amplifier and data were recorded with the g.Recorder software. Additional gel (GAMMAgel by g.tec) was applied to the channels after the cap was positioned to reduce impedances (<50 KΩ). EEG data were collected during the auditory task immediately before and after neurostimulation (Fig. 1*A*).

Neurostimulation. Two 5x5 cm^2 electrodes encased in saline soaked sponges were placed underneath the EEG head cap at the left auditory cortex (T7; International 10–20 System) and contralateral cheek. Stimulation was applied via battery-operated stimulator (Soterix Medical, New York, NY) for 10 min. In all conditions, stimulation consisted of 20 s of ramping up to the maximum current (1 mA) and 20 s of ramping down at the end of the 10-min period. Fifteen participants received 1 mA of 40-Hz tACS, 15 participants received 1 mA of tDCS, and 15 participants received sham stimulation, where the first 20 s ramped up to 1 mA then immediately ramped back down to create the sensation of stimulation. No sham participants indicated they were aware the stimulation ceased following the initial ramp-up period. The tACS group reported experiencing minor visual phosphenes, a known phenomenon reflecting the response of the retinae to tACS within particular frequency ranges (Matsumoto and Ugawa 2017; Schutter and Hortensius 2010), although 40 Hz is at the high end of frequencies that elicit phosphenes (Lorenz et al. 2019). The

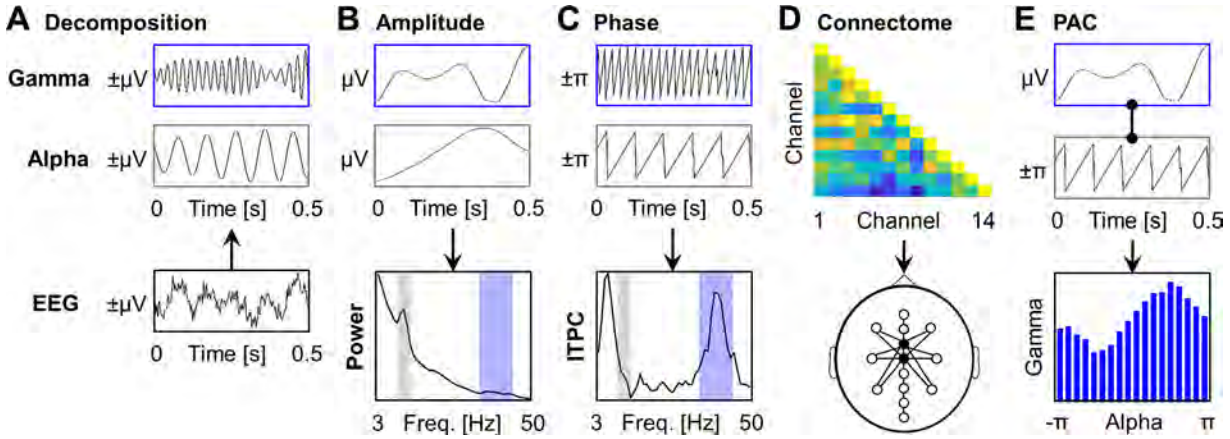

Fig. 2. Schematic illustration of EEG analyses. *A*: spectral decomposition. Electroencephalogram (EEG) data were separately filtered per frequency (3–50 Hz), with analyses performed on the gamma (40 Hz, *top*) and alpha (10 Hz, *bottom*) time series. Blue, gamma; gray, alpha. *B*: power analysis. Amplitude information was extracted at each frequency (Freq.) and squared to produce power. *C*: phase locking analysis. Phase information was extracted at each frequency for analysis of phase locking [intertrial phase coherence (ITPC)]. *D*: connectome analysis. Functional connectomes were quantified separately from amplitude- and phase-based measures of connectivity between all channel-by-channel pairs. Warmer colors represent greater connectivity between channel pairs and cooler colors represent less connectivity (*top*). Filled black circles indicate a frontocentral channel hub, with connections indicated by black lines between channels (*bottom*). *E*: phase-amplitude coupling (PAC) analysis. PAC was computed between alpha phase and gamma amplitude by measuring the divergence of the observed phase-amplitude distribution from the uniform distribution.

electrodes were removed after 10 min and EEG impedances were checked to ensure no channels were affected by the neurostimulation procedure. The head cap was not adjusted between EEG sessions and the position of the EEG channels remained constant. Current modeling was performed using the Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation (ROAST) software on the MNI-152 1mm standard head (Huang et al. 2018; Fig. 1*B*).

Auditory task. Participants placed two foam headphone ear inserts in their ears and indicated they were ready to begin. The auditory task consisted of 200 trials in which 40-Hz click trains (2-ms click every 25 ms, boxcar fashion) were presented binaurally at 75 dB for 500 ms with a 2,000-ms interstimulus interval (ISI; Legget et al. 2017; McFadden et al. 2014). Participants were instructed to sit still with their eyes open for the duration of the 7-min auditory click-train task. They completed two identical sessions of the auditory task while EEG data were recorded, immediately before and after neurostimulation (Fig. 1*A*).

Preprocessing. EEG data were passed through a 0.1- to 70-Hz two-pass Butterworth infinite impulse response (IIR) bandpass filter and 60-Hz line noise was removed using discrete Fourier transform. The outputs were manually inspected to reject any channels displaying artifactual signal (e.g., from poor contact) and segmented into nonoverlapping trials (−500 to +1,500 ms from click onset). Independent components analysis was performed on the remaining channels to remove electromyography and other artifacts (Hipp and Siegel 2013). Data were manually reinspected to reject any trials containing residual noise. All clean trials were analyzed (mean ± SD: 179 ± 21 trials/session).

Spectral decomposition. Spectral decomposition was performed per channel using a multitapering approach (Mitra and Pesaran 1999) with the FieldTrip toolbox (Oostenveld et al. 2011) for MATLAB (MathWorks Inc., Natick, MA). The 2-s data segments were zero-padded to 10 s, and the multitaper time-frequency spectrum was calculated by sliding a 500-ms window in 10-ms increments at each frequency from 3 to 50 Hz (1/4 fractional bandwidth, rounded up). Alpha time series were extracted directly from the outputs, centered at 10 Hz (4-Hz bandwidth). Gamma time series were recalculated by sliding a 300-ms window in 10-ms increments at 40 Hz (10-Hz bandwidth) to preserve the temporal resolution of higher-frequency responses.

Evoked power and phase locking. Evoked power (EP) and phase locking (intertrial phase coherence; ITPC) were computed from the amplitude and phase outputs of the multitaper time-frequency spectrum, respectively (Fig. 2*A*–*C*). Absolute EP was defined as the mean raw power across three nonoverlapping epochs: prestimulus (−250 to −50 ms from click onset), click-train, (0–500 ms from click onset), and ISI (700–1,200 ms from click onset). Normalized EP was defined as the change in poststimulus (0–1,250 ms from click onset) power relative to the prestimulus epoch (i.e., (poststimulus power − mean

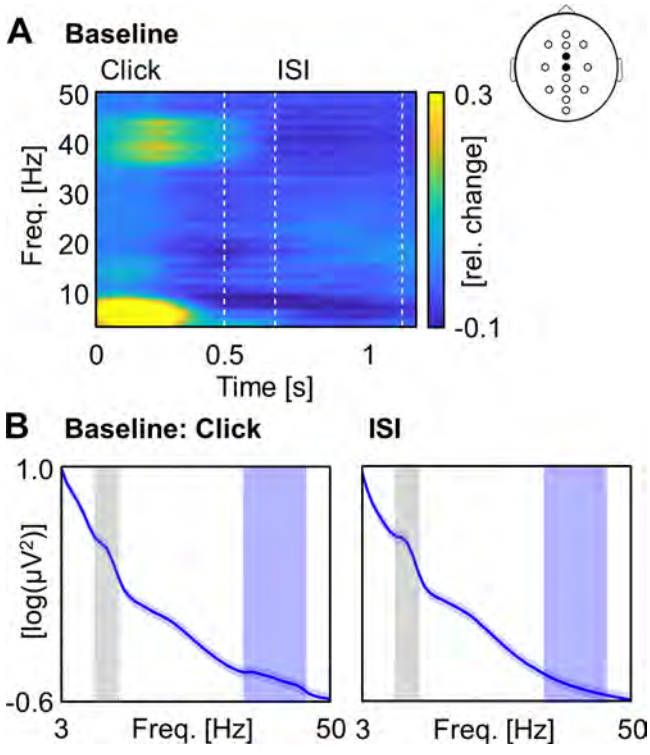

Fig. 3. Baseline evoked power (EP). *A*: grand mean baseline normalized EP at frontocentral channels (*inset*, filled in black). The auditory gamma response and low-frequency auditory-evoked potentials (AEP) were specific to the click-train epoch (0–500 ms from click onset). The interstimulus interval (ISI) epoch (700–1,200 from click onset) is marked for comparison. *B*: same data as *A* shown as means without normalization (i.e., absolute EP) during the 500-ms click-train (*left*) and ISI (*right*) epochs. Note the alpha peaks during both epochs. Blue, gamma; gray, alpha. Freq., frequency; rel., relative.

prestimulus power)/mean prestimulus power). ITPC was computed over the poststimulus epoch.

Graph theory. Amplitude and phase connectomes (AC and PC, respectively) were computed from the poststimulus time-series data using both amplitude- and phase-based functional connectivity measures following removal of the AEP. Amplitude connectivity was quantified using linear correlation independent of phase information, and phase connectivity was quantified as phase-locking values independent of amplitude information (Lachaux et al. 1999). Connectivity routines were performed on all channel pairs with the FieldTrip defaults (Oostenveld et al. 2011). The outputs were separately assessed for network degrees (i.e., the weight of connections between each channel and all other channels) using a threshold of 0.65 relative to the maximum of 1 (Fig. 2*D*).

Cross-frequency coupling. Phase-amplitude coupling (PAC) was quantified per channel using the modulation index method following removal of the AEP (Tort et al. 2010; Fig. 2*E*). The 2-s data segments were zero-padded to 10 s and separately bandpass filtered at the alpha (10-Hz center, 4-Hz bandwidth) and gamma (40-Hz center, 12-Hz bandwidth) frequencies using two-pass Butterworth IIR filters. Phase values were extracted from the alpha signal and amplitude values were extracted from the gamma signal using the Hilbert transform. PAC was computed separately from the click (0–500 ms from click onset) and ISI (700–1,200 ms from click onset) data segments of all trials for one session pooled together. For each set of trials, the phase values were pooled and divided into 18 bins, the amplitude values were averaged and normalized per phase bin, and PAC was calculated using Kullback-Leibler divergence. Outputs were *z*-score normalized on chance PAC distributions generated from the analysis of data permuted across trials (1,000 iterations; Aru et al. 2015; Tort et al. 2010). This procedure shuffles the timing of the amplitude envelope relative to the phase without altering the original data and thus eliminates differences in input data, including known differences in trial counts between data sets.

Statistics. All EEG measures were tested for 2 group (tACS or tDCS, sham) × 2 session (baseline, stimulation) interactions using Monte Carlo permutations with cluster-based correction for multiple comparisons (Maris and Oostenveld 2007). In addition, we directly compared tACS and tDCS groups using the same conventions. The click-train (0–500 ms from click onset) and ISI (700–1,200 ms from click onset) data segments were tested separately. For each interaction test, session effects were calculated as the difference between the stimulation and baseline data and input into the statistical test as a function of group. Clusters were formed in space and time by thresholding *t*-values at $P < 0.05$ using the maximum size criterion. Permutation distributions were generated by randomly shuffling group labels (1,000 iterations) and corrected *P* values were obtained by comparing the observed data to the random permutation distributions (e.g., 50 Type I errors out of 1,000 randomizations yields a *P* of 0.05). This is an extremely powerful approach because it recreates any biases in the data with each randomization and thus tests for effects without any assumption over where they may occur. Interaction effect sizes were then quantified by means of Cohen's d (i.e., (mean tACS or tDCS session effect − mean sham session effect)/pooled baseline SD; Morris 2008). Measures with significant interaction effects are displayed as normalized difference scores (i.e., (stimulation − baseline)/(stimulation + baseline)) to show the change from baseline while controlling for baseline variability.

RESULTS

Left auditory cortex stimulation reaches bilateral temporal lobes. Current modeling indicated that the neurostimulation applied between baseline and stimulation auditory task sessions maximally affected the targeted site (Fig. 1*B*). Anodal stimulation of left auditory cortex (T7) altered the electrical field in left temporal lobe and, to a lesser extent, right temporal lobe.

Gamma click trains induce auditory gamma responses. To confirm that the auditory click-train stimuli induced activity at 40 Hz (Legget et al. 2017; McFadden et al. 2014), we plotted the time-frequency representation of power for all subjects at baseline (3–50 Hz; see Fig. 2*B*). Figure 3*A* illustrates the normalized evoked power (EP) in frontocentral channels (McFadden et al. 2014), demonstrating a 40-Hz gamma response and a low-frequency response reflecting the AEP during the

Table 1. *Summary of all results*

			tACS > Sham		tDCS > Sham		tACS versus tDCS	
Frequency	Measure	Epoch	*P*	*d*	*P*	*d*	*P*	*d*
Gamma	Absolute EP	Prestim.	1		1		1	
	Normalized EP	Click	0.019*	0.906	>0.37		0.007*	1.267
		ISI	0.683		0.663		1	
	AC	Click	1		1		0.651	
		ISI	0.315		1		>0.76	
	ITPC	Click	0.044*	0.856	0.691		0.027*	1.198
		ISI	>0.37		>0.17		>0.42	
	PC	Click	0.046*	1.213	0.05*	0.941	1	
		ISI	0.05*	1.133	0.052*	0.957	1	
Alpha × gamma	PAC	Click	1		0.428		1	
		ISI	1		0.044*	0.517	0.0001*	0.445
Alpha	Absolute EP	Prestim.	1		0.121		1	
	Normalized EP	Click	0.754		>0.08		0.140	
		ISI	0.273		0.579		1	
	AC	Click	>0.21		0.489		>0.27	
		ISI	>0.27		>0.31		>0.29	
	ITPC	Click	1		0.15		>0.57	
		ISI	0.559		>0.59		0.154	
	PC	Click	>0.20		>0.30		>0.45	
		ISI	>0.30		>0.10		>0.4	

*Effect sizes (Cohen's *d*) are provided for significant interactions after cluster-based correction for multiple comparisons. AC, amplitude connectome; EP, evoked power; ISI, interstimulus interval; ITPC, intertrial phase coherence; PAC, phase-amplitude coupling; PC, phase connectome; Prestim., prestimulus; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation.

500-ms click-train epoch. Figure 3*B* shows the mean absolute EP in the same channels, demonstrating a 40-Hz gamma peak and a 10-Hz alpha peak during the 500-ms click-train epoch. Note that the gamma peak was specific to the click-train epoch, whereas the alpha peak persisted during the ISI.

Neurostimulation does not affect prestimulus evoked power. The effects of tACS and tDCS were investigated on raw EEG activity at the 40-Hz frequency entrained via tACS. There were no effects of neurostimulation on prestimulus absolute EP (tACS > sham $P = 1$, tDCS > sham $P = 1$; tACS versus tDCS $P = 1$; Table 1).

tACS increases auditory stimulus-evoked power. The effects of tACS and tDCS were investigated on stimulus-evoked 40-Hz activity. Figure 4, *A* and *B* illustrates normalized EP at baseline, demonstrating a clear auditory gamma response. Both mean and single-subject EP time series constrain the duration of the auditory response to the click-train epoch (Legget et al. 2017; McFadden et al. 2014). There was a significant effect of tACS on the auditory response (tACS > sham click $P = 0.019$, $d = 0.906$; tACS > tDCS click $P = 0.007$, $d = 1.267$; Fig. 4, *C* and *D*, Table 1) that did not persist after termination of the click trains (tACS > sham ISI $P = 0.683$; tACS > tDCS ISI $P = 1$). There were no significant effects of tDCS on normalized EP (tDCS > sham click $P > 0.37$, ISI $P = 0.663$).

Neurostimulation does not affect the amplitude connectome. Having demonstrated that gamma tACS increased EP during the click trains (Fig. 4), we next investigated the effects of tACS and tDCS on the 40-Hz amplitude connectome (AC; see Fig. 2*D*). There were no significant effects on the AC (tACS > sham click $P = 1$, ISI $P = 0.315$; tDCS > sham click $P = 1$, ISI $P = 1$; tACS versus tDCS click $P = 0.651$, ISI $P > 0.76$; Table 1). Thus, gamma tACS increased per-channel stimulus-related EP but not the strength of amplitude-based functional connections between channels. tDCS affected neither per-channel EP nor the AC.

Gamma click trains induce gamma phase locking to the auditory stimulus. To confirm that the auditory click-train stimuli reset oscillatory activity at 40 Hz (Legget et al. 2017; McFadden et al. 2014), we plotted the time-frequency representation of ITPC (Tallon-Baudry et al. 1996) for all subjects at baseline (3–50 Hz; see Fig. 2*C*). Figure 5*A* illustrates phase locking to the auditory stimulus in frontocentral channels (McFadden et al. 2014), demonstrating a 40-Hz gamma response and a low-frequency response reflecting the AEP during the 500-ms click-train epoch. Figure 5*B* shows the mean phase locking in the same channels, demonstrating phase locking specific to the click-train epoch.

tACS increases phase locking to the auditory stimulus. The effects of tACS and tDCS were investigated on 40-Hz phase locking, as measured by ITPC (Tallon-Baudry et al. 1996). Figure 6, *A* and *B* illustrates gamma ITPC at baseline, further demonstrating a clear auditory gamma response and constraining the duration of the response to the click-train epoch (Legget et al. 2017; McFadden et al. 2014). There was a significant

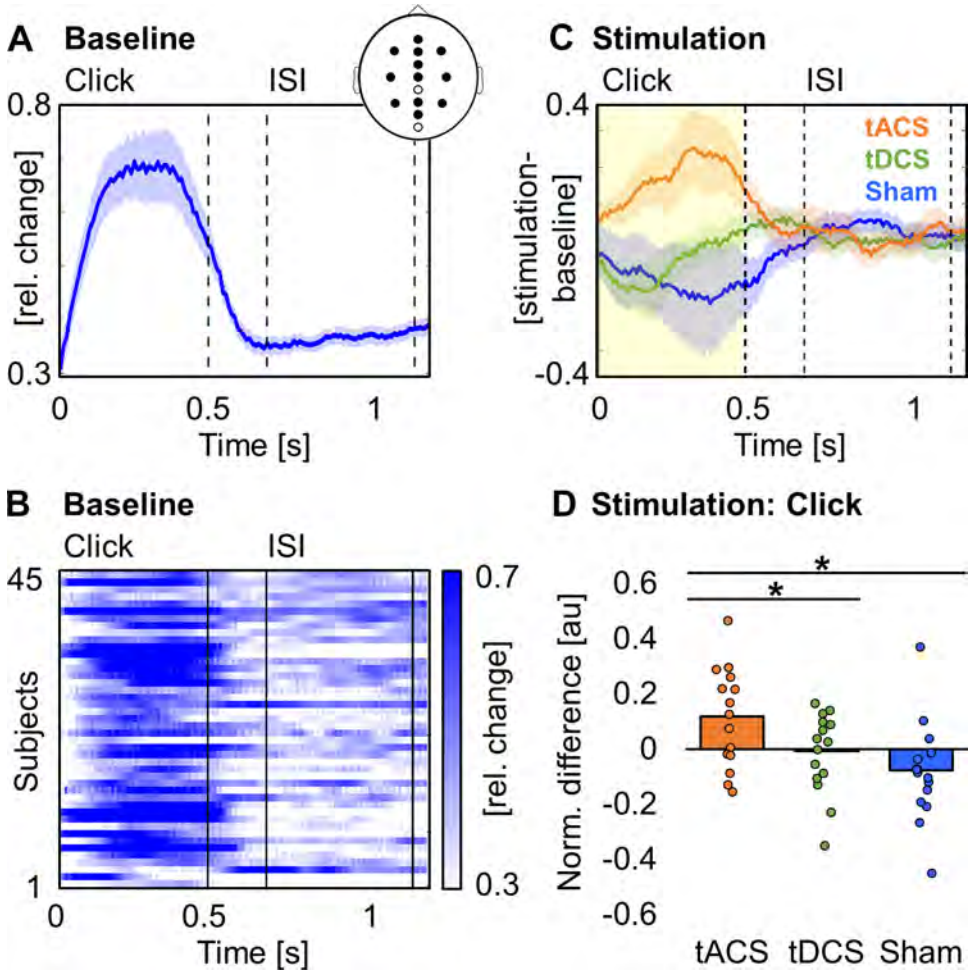

Fig. 4. Transcranial alternating current stimulation (tACS) increases auditory gamma evoked power (EP). *A*: grand mean baseline gamma EP time series across the channels affected by tACS (*inset*, filled in black). The auditory response was specific to the click-train epoch (0–500 ms from click onset). The interstimulus interval (ISI) epoch (700–1,200 ms from click onset) is marked for comparison. Shading, SE. *B*: same data as *A* shown per subject for all 45 subjects to emphasize the intersubject reliability of the auditory response. *C*: gamma tACS increased the auditory response relative to baseline across most of the topography, as shown in the *inset* in *A*. Shading, SE; yellow, epoch of significant interaction. *D*: same data as *C* shown as normalized (Norm.) difference scores to correct for baseline variability. *Significant interaction; au, arbitrary unit. rel., Relative; tDCS, transcranial direct current stimulation.

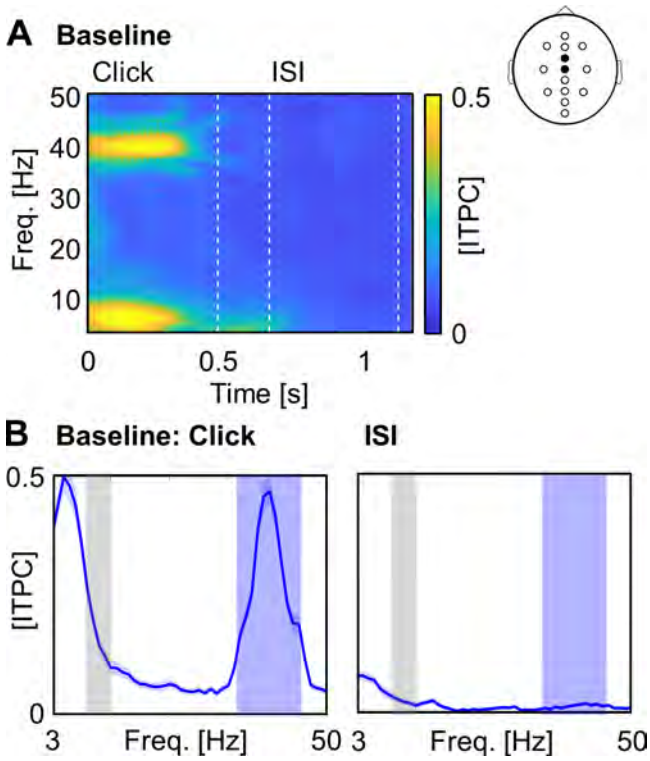

Fig. 5. Baseline intertrial phase coherence (ITPC). *A*: grand mean baseline ITPC at frontocentral channels (*inset*, filled in black). The auditory gamma response and low-frequency auditory-evoked potentials (AEP) were specific to the click-train epoch (0–500 ms from click onset). The interstimulus interval (ISI) epoch (700–1,200 from click onset) is marked for comparison. *B*: same data as *A* shown as means during the 500-ms click-train (*left*) and ISI (*right*) epochs to show the specificity of phase locking to the auditory stimulus. Blue, gamma; gray, alpha. Freq., frequency.

effect of tACS on the auditory response (tACS > sham click $P = 0.044$, $d = 0.856$; tACS > tDCS click $P = 0.027$, $d = 1.198$; Fig. 6, *C* and *D*, Table 1) that did not persist after termination of the click trains (tACS > sham ISI $P > 0.37$; tACS > tDCS ISI $P > 0.42$). There were no significant effects of tDCS on ITPC (tDCS > sham click $P = 0.691$, ISI $P > 0.17$).

Both tACS and tDCS strengthen the phase connectome. Having demonstrated that gamma tACS increased phase locking during the click trains (Fig. 6), we next investigated the effects of tACS and tDCS on the 40-Hz phase connectome (PC; see Fig. 2*D*). There was a significant effect of tACS on the PC during the click trains (tACS > sham click $P = 0.046$, $d = 1.213$; Fig. 7, *A–C*, Table 1) that persisted after termination of the click trains (ISI $P = 0.05$, $d = 1.133$). There was also a significant effect of tDCS on the PC during the click trains (tDCS > sham click $P = 0.05$, $d = 0.941$; Fig. 7, *D–F*) that persisted after termination of the click trains (ISI $P = 0.052$, $d = 0.957$). Thus, gamma tACS increased per-channel phase locking and the strength of phase-based functional connections between channels. tDCS increased only the strength of phase-based functional connections between channels. tACS and tDCS had equal effects on the PC (all $P = 1$).

tDCS strengthens alpha-gamma coupling during the ISI. Having demonstrated peaks in the power spectrum at both 10 and 40 Hz during the auditory task (Fig. 3*B*), we next investigated the effects of tACS and tDCS on cross-frequency coupling between 10-Hz phase and 40-Hz amplitude (PAC). Figure 8*A* illustrates alpha-gamma PAC at baseline, demonstrating PAC after termination of the click trains, but not during the auditory stimulus. There were no effects of gamma tACS on PAC (tACS > sham click $P = 1$, ISI $P = 1$; Table 1). There was a modest effect of tDCS on PAC after termination of the click trains (tDCS > sham ISI $P = 0.044$, $d = 0.517$; tDCS > tACS ISI $P = 0.0001$, $d = 0.445$; Fig. 8, *B* and *C*), but no effect during the click trains (tDCS > sham click $P = 0.428$; tDCS > tACS click $P = 1$). Thus, tDCS increased non-auditory-evoked PAC.

Neurostimulation does not affect induced alpha responses. To confirm the specificity of effects to auditory gamma responses, we investigated the effects of tACS and tDCS on the induced 10-Hz alpha oscillation (see Fig. 3*B*). There were no significant effects of tACS or tDCS on alpha power, ITPC, or functional connectivity (all $P > 0.08$). All results are reported in Table 1.

DISCUSSION

This study systematically investigated the aftereffect of two different noninvasive neurostimulation techniques on gamma activity during a passive auditory task. Contrary to reports that transcranial alternating current stimulation (tACS) has little persisting offline effect (Stecher and Herrmann 2018), the results revealed offline effects in multiple metrics of the stimulus-related gamma response. Gamma tACS increased both gamma evoked power (EP) and phase locking (intertrial phase coherence; ITPC) to the auditory stimulus compared with sham stimulation and transcranial direct current stimulation (tDCS), but only during the click trains and not during the interstimulus interval (ISI). There were no significant effects in absolute EP before stimulus presentation. These temporally distinct findings demonstrate the specificity of offline tACS to affect neural responses evoked by a frequency-tuned external stimulus (Heise et al. 2019). These results suggest that frequency-tuned tACS can be a valuable tool to target oscillatory biomarkers associated with excitatory/inhibitory (E/I) imbalance in autism spectrum disorder (ASD), schizophrenia, and bipolar disorder.

Disruption of the functional connectome is also observed in many neuropsychiatric disorders, linking ASD, schizophrenia, and bipolar disorder to abnormal neural interactions across spatial scales (de Lange et al. 2019; Steinmann et al. 2014b; reviewed in van den Heuvel and Sporns 2019). Here, both tACS and tDCS strengthened the gamma phase connectome (PC) compared with sham stimulation, and effects persisted through the auditory click trains and ISI. These results extend previous reports of changes in functional or resting-state connectivity during and following tDCS (Kunze et al. 2016; Polanía et al. 2011a, 2011b) and tACS (Kar et al. 2020; Meier et al. 2019; Onoda et al. 2017; Preisig et al. 2020) by suggesting that both techniques strengthen communication across spatial scales. Furthermore, these findings establish that transcranial electrical stimulation elicits offline changes in the functional gamma PC even in the absence of stimulus-related phase locking within channels. As there were no changes in the gamma amplitude connectome (AC), these findings further show that neurostimulation affects the connectome by way of affecting the relative timing, but not magnitude, of neural activity between cortical areas.

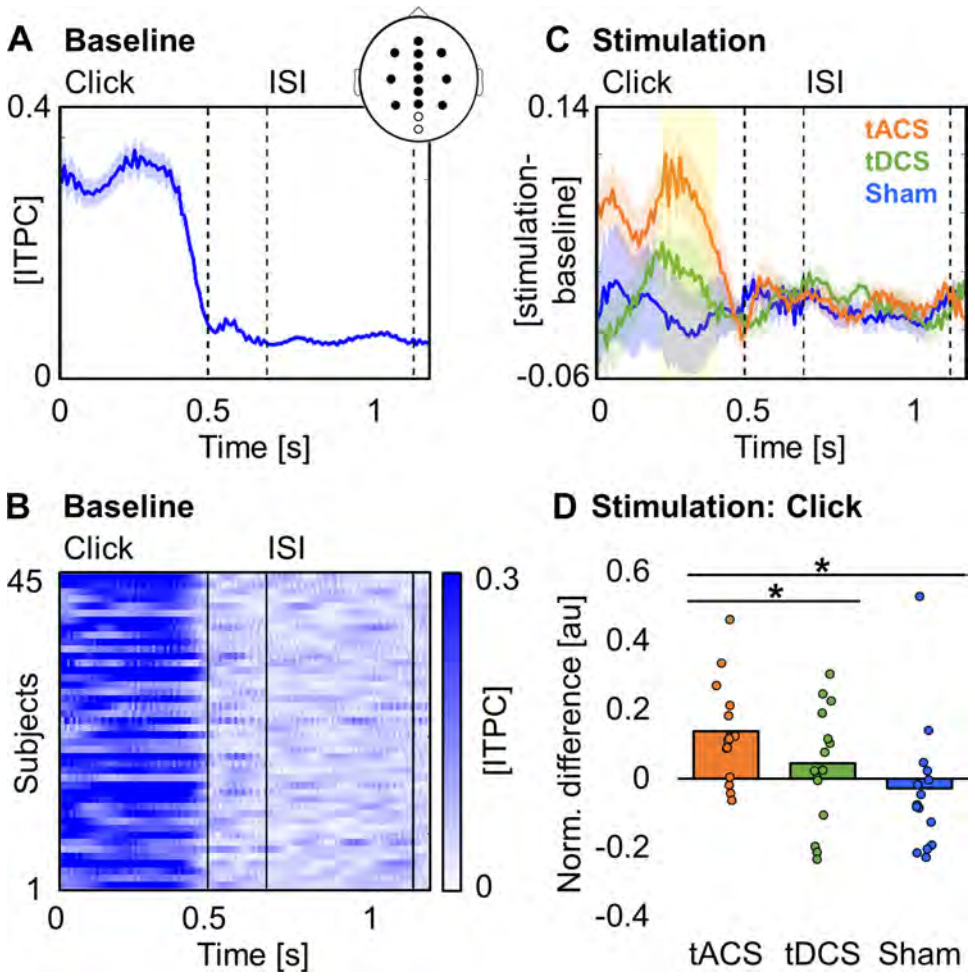

Fig. 6. Transcranial alternating current stimulation (tACS) increases auditory gamma intertrial phase coherence (ITPC). *A*: grand mean baseline gamma ITPC time series across the channels affected by tACS (*inset*, filled in black). The auditory response was specific to the click-train epoch (0–500 ms from click onset). The interstimulus interval (ISI) epoch (700–1,200 ms from click onset) is marked for comparison. Shading, SE. *B*: same data as *A* shown per subject for all 45 subjects to emphasize the intersubject reliability of the auditory response. *C*: gamma tACS increased the auditory response relative to baseline across most of the topography, as shown in the *inset* in *A*. Shading, SE; yellow, epoch of significant interaction. *D*: same data as *C* shown as normalized difference scores to correct for baseline variability. *Significant interaction; au, arbitrary unit. tDCS, transcranial alternating current stimulation.

Disrupted cross-frequency coupling to gamma activity (PAC) also correlates with disordered behavior, linking ASD (Khan et al. 2013), schizophrenia (Hirano et al. 2018), and Parkinson's disease (Meidahl et al. 2019) to abnormal neural interactions across temporal scales (reviewed in Bonnefond et al. 2017; Canolty and Knight 2010). Here, we observed no increase in the coupling of auditory-evoked gamma activity to the dominant alpha oscillatory rhythm with tDCS or tDCS. However, there was a modest increase in alpha-gamma PAC in frontocentral channels during the ISI following tDCS as compared with both sham and gamma tACS. This effect was not observed with tACS, consistent with previous reports in the literature (Helfrich et al. 2016). This finding joins a short list of studies reporting that tDCS affects offline EEG measures (Jones et al. 2017, 2020; Krause et al. 2017; McDermott et al. 2019).

Finally, there were no significant effects of either neurostimulation technique on measures of power, phase locking, or the functional connectome in the alpha band, suggesting gamma frequency specificity per the auditory task. Indeed, the observation that tDCS did not affect the alpha PC, even though the technique is not frequency specific, further suggests that both transcranial electrical stimulation methods affected the gamma PC according to the timing of the 40-Hz click-train task.

Understanding how tACS and tDCS modulate different EEG correlates of disordered behavior is necessary to develop neurostimulation therapies that meet the needs of patients with different disorders. There are several limitations that may limit the generalizability of the present results to clinical populations. First, participants were all neurotypical college-aged students. We therefore provide a proof of concept of the effects of neurostimulation on gamma biomarkers, but not a direct test on clinical samples with abnormal baseline measures. Second, stimulation of left auditory cortex at T7 elicited bilateral electrical field effects. It is possible that focal high-definition neurostimulation would more precisely target specific anatomical substrates of clinical biomarkers, such as left auditory cortex. Furthermore, there exists the possibility that tACS drove neural entrainment through stimulation of peripheral nerves in the skin (Asamoah et al. 2019), which in turn drove cortical entrainment. The use of a more focal stimulation montage may also reduce the potential for unintended peripheral stimulation effects. Third, our EEG montage measured the frontocentral auditory response. It is possible that high-density EEG or MEG with lateral temporal channels would more effectively detect focal effects, such as those that may be stronger in left auditory cortex (Legget et al. 2017). Fourth, we applied 1 mA of tACS or tDCS and observed effects in several EEG metrics, but note that higher doses may elicit stronger effects (Chew et al. 2015; Preisig et al. 2020). Fifth, different neurostimulation techniques may differentially affect participant alertness (McIntire et al. 2014), which may affect the auditory-evoked response. Lastly, the auditory task lasted 7

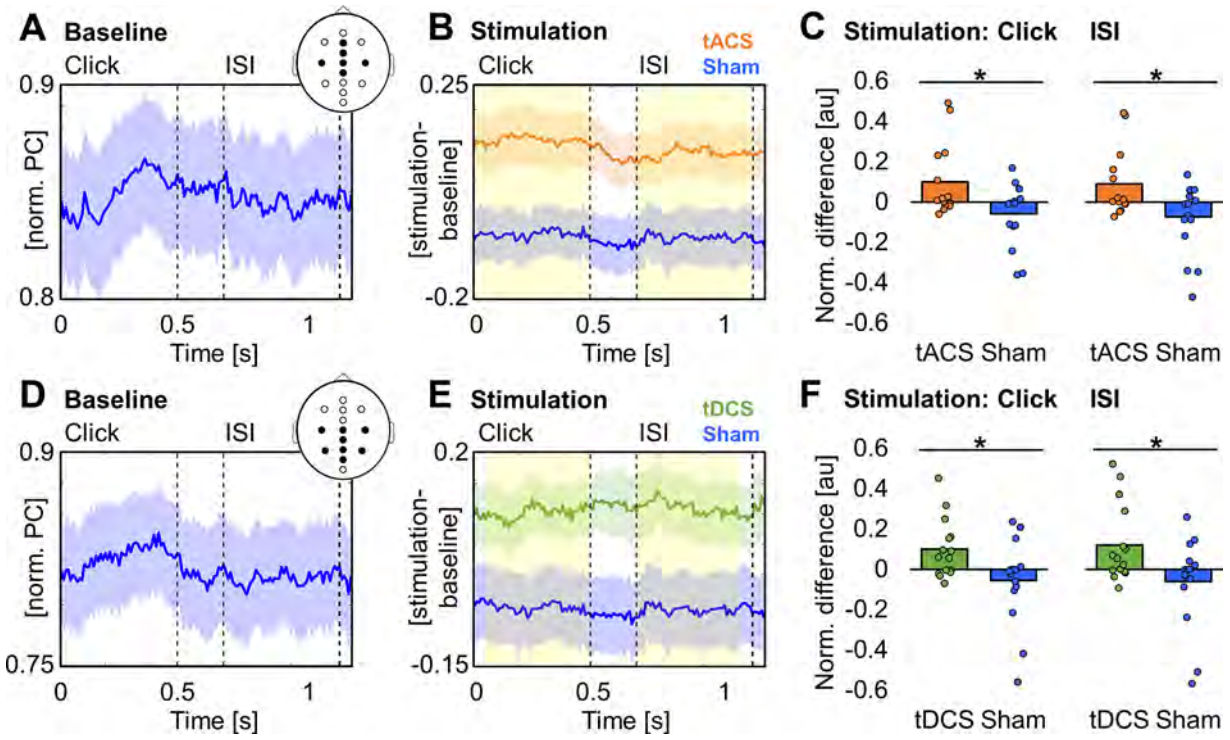

Fig. 7. Transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS) strengthen the gamma phase connectome (PC). *A*: grand mean baseline gamma PC time series across the channels affected by tACS (*inset*, filled in black). Vertical lines indicate the click-train and interstimulus interval (ISI) epochs. Shading, SE. *B*: gamma tACS strengthened the PC in frontocentral channels, as shown in the *inset* in *A*, throughout the click trains and ISI. Shading, SE; yellow, epochs of significant interaction. *C*: same data as *B* shown as normalized (Norm.) difference scores to correct for baseline variability. *Significant interaction. *D*: grand mean baseline gamma PC time series across the channels affected by tDCS (*inset*, filled in black), same conventions as *A*. *E*: tDCS strengthened the PC in central-posterior channels, as shown in the *inset* in *D*, throughout the click trains and ISI, same conventions as *B*. *F*: same data as *E* shown as normalized difference scores to correct for baseline variability, same conventions as *C*.

min, limiting interpretation of how long neurostimulation effects may persist in longer tasks. Future studies should address these limitations and investigate the duration of offline gamma effects in different clinical samples.

In conclusion, we provide a comprehensive account of the effects of two different noninvasive electrical neurostimulation techniques on auditory gamma-band responses, a common biomarker of several clinical disorders. The results reveal that auditory gamma responses, which are disrupted in ASD (Gandal et al. 2010; Grice et al. 2001; Rojas et al. 2008; Rojas and Wilson 2014; Sun et al. 2012; Wilson et al. 2007), schizophrenia (Edgar et al. 2014; Krishnan et al. 2009), and bipolar disorder (Maharajh et al. 2007), can be increased following 10 min of frequency-tuned tACS to left auditory cortex. tACS increased gamma EP and phase locking to the auditory click trains. These effects were specific to 40-Hz tACS, and not depolarizing anodal tDCS to the same site, revealing that frequency-tuned tACS adjusts both the magnitude and timing of the auditory gamma response. However, both tACS and tDCS strengthened the gamma PC, and effects persisted through the ISI with no change in the gamma AC, suggesting that neurostimulation synchronizes the relative timing of

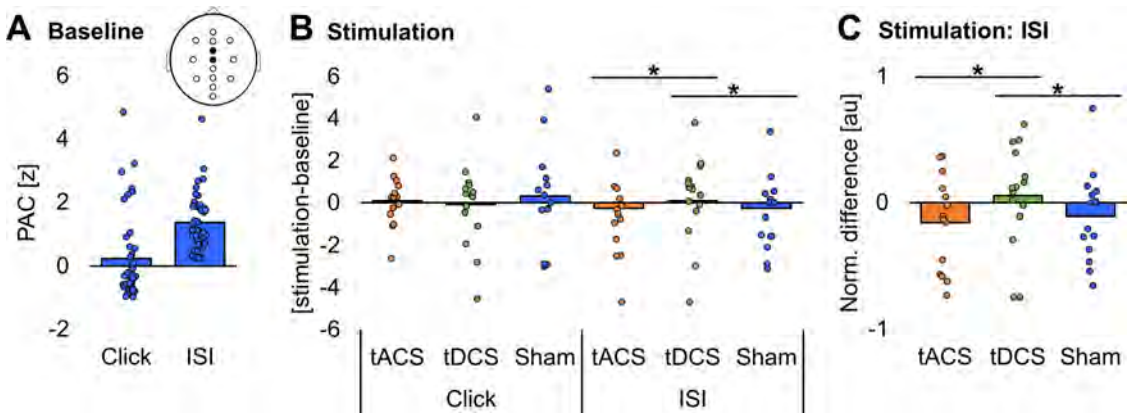

Fig. 8. Transcranial direct current stimulation (tDCS) strengthens nonauditory alpha-gamma phase-amplitude coupling (PAC). *A*: baseline PAC across the channels affected by tDCS (*inset*, filled in black). *B*: tDCS strengthened PAC in frontocentral channels, as shown in the *inset* in *A*, during the ISI. There were no significant effects during the click trains. *Significant interaction. *C*: same data as *B* shown as normalized differences scores to correct for baseline variability, same conventions as *B*. tACS, transcranial alternating current stimulation.

activity between cortical areas regardless of the specific stimulation mechanism. Finally, tDCS, but not tACS, increased alpha-gamma PAC in the absence of auditory stimuli, implying a lasting increase in interactions across temporal scales following tDCS. Together, the results of the present study reveal dissociable neurophysiological changes following two neurostimulation techniques commonly applied in research and clinical settings, and demonstrate how noninvasive neurostimulation may be used to target EEG/MEG biomarkers of disordered behavior.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.T.J. and D.R. conceived and designed research; K.T.J., E.L.J., and Z.S.T. performed experiments; K.T.J., E.L.J., and Z.S.T. analyzed data; K.T.J., E.L.J., and Z.S.T. interpreted results of experiments; K.T.J., E.L.J., and Z.S.T. prepared figures; K.T.J., E.L.J., and Z.S.T. drafted manuscript.

REFERENCES

Amatachaya A, Auvichayapat N, Patjanasoontorn N, Suphakunpinyo C, Ngernyam N, Aree-Uea B, Keeratitanont K, Auvichayapat P. Effect of anodal transcranial direct current stimulation on autism: a randomized double-blind crossover trial. *Behav Neurol* 2014: 173073, 2014. doi:10.1155/2014/173073.

Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Invest Ophthalmol Vis Sci* 45: 702–707, 2004. doi:10.1167/iovs.03-0688.

Aru J, Aru J, Priesemann V, Wibral M, Lana L, Pipa G, Singer W, Vicente R. Untangling cross-frequency coupling in neuroscience. *Curr Opin Neurobiol* 31: 51–61, 2015. doi:10.1016/j.conb.2014.08.002.

Asamoah B, Khatoun A, Mc Laughlin M. tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nat Commun* 10: 266, 2019. doi:10.1038/s41467-018-08183-w.

Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. *Stroke* 41: 1229–1236, 2010. doi:10.1161/STROKEAHA.109.576785.

Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, Fregni F. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J Neurol Sci* 249: 31–38, 2006. doi:10.1016/j.jns.2006.05.062.

Bonnefond M, Kastner S, Jensen O. Communication between brain areas based on nested oscillations. *eNeuro* 4: ENEURO.0153-16.2017, 2017. doi:10.1523/ENEURO.0153-16.2017.

Brunoni AR, Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Boggio PS, Giacopuzzi M, Barbieri S, Priori A. Transcranial direct current stimulation (tDCS) in unipolar vs. bipolar depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 35: 96–101, 2011. doi:10.1016/j.pnpbp.2010.09.010.

Buzsáki G, Wang XJ. Mechanisms of gamma oscillations. *Annu Rev Neurosci* 35: 203–225, 2012. doi:10.1146/annurev-neuro-062111-150444.

Canolty RT, Knight RT. The functional role of cross-frequency coupling. *Trends Cogn Sci* 14: 506–515, 2010. doi:10.1016/j.tics.2010.09.001.

Chew T, Ho KA, Loo CK. Inter- and intra-individual variability in response to transcranial direct current stimulation (tDCS) at varying current intensities. *Brain Stimul* 8: 1130–1137, 2015. doi:10.1016/j.brs.2015.07.031.

Davis H, Mast T, Yoshie N, Zerlin S. The slow response of the human cortex to auditory stimuli: recovery process. *Electroencephalogr Clin Neurophysiol* 21: 105–113, 1966. doi:10.1016/0013-4694(66)90118-0.

Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics* 125: e17–e23, 2010. doi:10.1542/peds.2009-0958.

de Lange SC, Scholtens LH; Alzheimer's Disease Neuroimaging Initiative, van den Berg LH, Boks MP, Bozzali M, Cahn W, Dannlowski U, Durston S, Geuze E, van Haren NEM, Hillegers MHJ, Koch K, Jurado MÁ, Mancini M, Marqués-Iturria I, Meinert S, Ophoff RA, Reess TJ, Repple J, Kahn RS, van den Heuvel MP. Shared vulnerability for connectome alterations across psychiatric and neurological brain disorders. *Nat Hum Behav* 3: 988–998, 2019. doi:10.1038/s41562-019-0659-6.

Dinstein I, Pierce K, Eyler L, Solso S, Malach R, Behrmann M, Courchesne E. Disrupted neural synchronization in toddlers with autism. *Neuron* 70: 1218–1225, 2011. doi:10.1016/j.neuron.2011.04.018.

Edgar JC, Chen YH, Lanza M, Howell B, Chow VY, Heiken K, Liu S, Wootton C, Hunter MA, Huang M, Miller GA, Cañive JM. Cortical thickness as a contributor to abnormal oscillations in schizophrenia? *Neuroimage Clin* 4: 122–129, 2014. doi:10.1016/j.nicl.2013.11.004.

Edgar JC, Fisk CL IV, Liu S, Pandey J, Herrington JD, Schultz RT, Roberts TP. Translating adult electrophysiology findings to younger patient populations: difficulty measuring 40-Hz auditory steady-state responses in typically developing children and children with autism spectrum disorder. *Dev Neurosci* 38: 1–14, 2016. doi:10.1159/000441943.

Edgar JC, Khan SY, Blaskey L, Chow VY, Rey M, Gaetz W, Cannon KM, Monroe JF, Cornew L, Qasmieh S, Liu S, Welsh JP, Levy SE, Roberts TP. Neuromagnetic oscillations predict evoked-response latency delays and core language deficits in autism spectrum disorders. *J Autism Dev Disord* 45: 395–405, 2015. doi:10.1007/s10803-013-1904-x.

Elsabbagh M, Volein A, Csibra G, Holmboe K, Garwood H, Tucker L, Krljes S, Baron-Cohen S, Bolton P, Charman T, Baird G, Johnson MH. Neural correlates of eye gaze processing in the infant broader autism phenotype. *Biol Psychiatry* 65: 31–38, 2009. doi:10.1016/j.biopsych.2008.09.034.

Erickson CA, Veenstra-Vanderweele JM, Melmed RD, McCracken JT, Ginsberg LD, Sikich L, Scahill L, Cherubini M, Zarevics P, Walton-Bowen K, Carpenter RL, Bear MF, Wang PP, King BH. STX209 (arbaclofen) for autism spectrum disorders: an 8-week open-label study. *J Autism Dev Disord* 44: 958–964, 2014. doi:10.1007/s10803-013-1963-z.

Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, Cogiamanian F, Barbieri S, Scarpini E, Priori A. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology* 71: 493–498, 2008. doi:10.1212/01.wnl.0000317060.43722.a3.

Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, Rigonatti SP, Marcolin MA, Freedman SD, Nitsche MA, Pascual-Leone A. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport* 16: 1551–1555, 2005. doi:10.1097/01.wnr.0000177010.44602.5e.

Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. *Bipolar Disord* 8: 203–204, 2006. doi:10.1111/j.1399-5618.2006.00291.x.

Fridriksson J, Richardson JD, Baker JM, Rorden C. Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. *Stroke* 42: 819–821, 2011. doi:10.1161/STROKEAHA.110.600288.

Gandal MJ, Edgar JC, Ehrlichman RS, Mehta M, Roberts TP, Siegel SJ. Validating γ oscillations and delayed auditory responses as translational biomarkers of autism. *Biol Psychiatry* 68: 1100–1106, 2010. doi:10.1016/j.biopsych.2010.09.031.

Gómez L, Vidal B, Maragoto C, Morales LM, Berrillo S, Vera Cuesta H, Baez M, Denis M, Marín T, Cabrera Y, Sánchez A, Alarcón C, Selguera M, Llanez Y, Dieguez L, Robinson M. Non-invasive brain stimulation for children with autism spectrum disorders: a short-term outcome study. *Behav Sci (Basel)* 7: 63, 2017. doi:10.3390/bs7030063.

Grice SJ, Spratling MW, Karmiloff-Smith A, Halit H, Csibra G, de Haan M, Johnson MH. Disordered visual processing and oscillatory brain activity in autism and Williams syndrome. *Neuroreport* 12: 2697–2700, 2001. doi:10.1097/00001756-200108280-00021.

Heimrath K, Fiene M, Rufener KS, Zaehle T. Modulating human auditory processing by transcranial electrical stimulation. *Front Cell Neurosci* 10: 53, 2016. doi:10.3389/fncel.2016.00053.

Heise KF, Monteiro TS, Leunissen I, Mantini D, Swinnen SP. Distinct online and offline effects of alpha and beta transcranial alternating current

stimulation (tACS) on continuous bimanual performance and task-set switching. *Sci Rep* 9: 3144, 2019. doi:10.1038/s41598-019-39900-0.

Helfrich RF, Herrmann CS, Engel AK, Schneider TR. Different coupling modes mediate cortical cross-frequency interactions. *Neuroimage* 140: 76–82, 2016. doi:10.1016/j.neuroimage.2015.11.035.

Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. *Front Hum Neurosci* 7: 279, 2013. doi:10.3389/fnhum.2013.00279.

Hipp JF, Siegel M. Dissociating neuronal gamma-band activity from cranial and ocular muscle activity in EEG. *Front Hum Neurosci* 7: 338, 2013. doi:10.3389/fnhum.2013.00338.

Hirano S, Nakhnikian A, Hirano Y, Oribe N, Kanba S, Onitsuka T, Levin M, Spencer KM. Phase-Amplitude Coupling of the Electroencephalogram in the Auditory Cortex in Schizophrenia. *Biol Psychiatry Cogn Neurosci Neuroimaging* 3: 69–76, 2018. doi:10.1016/j.bpsc.2017.09.001.

Huang Y, Datta A, Bikson M, Parra LC. ROAST: an open-source, fully-automated, realistic volumetric-approach-based simulator for TES. *Conf Proc IEEE Eng Med Biol Soc* 2018: 3072–3075, 2018. doi:10.1109/EMBC.2018.8513086.

Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci* 4: 186, 2010. doi:10.3389/fnhum.2010.00186.

Jones KT, Johnson EL, Berryhill ME. Frontoparietal theta-gamma interactions track working memory enhancement with training and tDCS. *Neuroimage* 211: 116615, 2020. doi:10.1016/j.neuroimage.2020.116615.

Jones KT, Peterson DJ, Blacker KJ, Berryhill ME. Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. *Brain Res* 1667: 28–40, 2017. doi:10.1016/j.brainres.2017.05.005.

Kar K, Ito T, Cole MW, Krekelberg B. Transcranial alternating current stimulation attenuates BOLD adaptation and increases functional connectivity. *J Neurophysiol* 123: 428–438, 2020. doi:10.1152/jn.00376.2019.

Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimul* 5: 155–162, 2012. doi:10.1016/j.brs.2011.02.007.

Khan S, Gramfort A, Shetty NR, Kitzbichler MG, Ganesan S, Moran JM, Lee SM, Gabrieli JDE, Tager-Flusberg HB, Joseph RM, Herbert MR, Hämäläinen MS, Kenet T. Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proc Natl Acad Sci USA* 110: 3107–3112, 2013. doi:10.1073/pnas.1214533110.

Kim DY, Ohn SH, Yang EJ, Park CI, Jung KJ. Enhancing motor performance by anodal transcranial direct current stimulation in subacute stroke patients. *Am J Phys Med Rehabil* 88: 829–836, 2009. doi:10.1097/PHM.0b013e3181b811e3.

Krause MR, Zanos TP, Csorba BA, Pilly PK, Choe J, Phillips ME, Datta A, Pack CC. Transcranial direct current stimulation facilitates associative learning and alters functional connectivity in the primate brain. *Curr Biol* 27: 3086–3096.e3, 2017.

Krishnan GP, Hetrick WP, Brenner CA, Shekhar A, Steffen AN, O'Donnell BF. Steady state and induced auditory gamma deficits in schizophrenia. *Neuroimage* 47: 1711–1719, 2009. doi:10.1016/j.neuroimage.2009.03.085.

Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation changes resting state functional connectivity: a large-scale brain network modeling study. *Neuroimage* 140: 174–187, 2016. doi:10.1016/j.neuroimage.2016.02.015.

Kutchko KM, Fröhlich F. Emergence of metastable state dynamics in interconnected cortical networks with propagation delays. *PLOS Comput Biol* 9: e1003304, 2013. doi:10.1371/journal.pcbi.1003304.

Lachaux JP, Rodriguez E, Martinerie J, Varela FJ. Measuring phase synchrony in brain signals. *Hum Brain Mapp* 8: 194–208, 1999. doi:10.1002/(SICI)1097-0193(1999)8:4<194:AID-HBM4>3.0.CO;2-C.

Legget KT, Hild AK, Steinmetz SE, Simon ST, Rojas DC. MEG and EEG demonstrate similar test-retest reliability of the 40Hz auditory steady-state response. *Int J Psychophysiol* 114: 16–23, 2017. doi:10.1016/j.ijpsycho.2017.01.013.

Lorenz R, Simmons LE, Monti RP, Arthur JL, Limal S, Laakso I, Leech R, Violante IR. Efficiently searching through large tACS parameter spaces using closed-loop Bayesian optimization. *Brain Stimul* 12: 1484–1489, 2019. doi:10.1016/j.brs.2019.07.003.

Maharajh K, Abrams D, Rojas DC, Teale P, Reite ML. Auditory steady state and transient gamma band activity in bipolar disorder. *Int Congr Ser* 1300: 707–710, 2007. doi:10.1016/j.ics.2006.12.073.

Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods* 164: 177–190, 2007. doi:10.1016/j.jneumeth.2007.03.024.

Matsumoto H, Ugawa Y. Adverse events of tDCS and tACS: a review. *Clin Neurophysiol Pract* 2: 19–25, 2017. doi:10.1016/j.cnp.2016.12.003.

McDermott TJ, Wiesman AI, Mills MS, Spooner RK, Coolidge NM, Proskovec AL, Heinrichs-Graham E, Wilson TW. tDCS modulates behavioral performance and the neural oscillatory dynamics serving visual selective attention. *Hum Brain Mapp* 40: 729–740, 2019. doi:10.1002/hbm.24405.

McFadden KL, Steinmetz SE, Carroll AM, Simon ST, Wallace A, Rojas DC. Test-retest reliability of the 40 Hz EEG auditory steady-state response. *PLoS One* 9: e85748, 2014. doi:10.1371/journal.pone.0085748.

McIntire LK, McKinley RA, Goodyear C, Nelson J. A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. *Brain Stimul* 7: 499–507, 2014. doi:10.1016/j.brs.2014.04.008.

Meidahl AC, Moll CKE, van Wijk BCM, Gulberti A, Tinkhauser G, Westphal M, Engel AK, Hamel W, Brown P, Sharott A. Synchronised spiking activity underlies phase amplitude coupling in the subthalamic nucleus of Parkinson's disease patients. *Neurobiol Dis* 127: 101–113, 2019. doi:10.1016/j.nbd.2019.02.005.

Meier J, Nolte G, Schneider TR, Engel AK, Leicht G, Mulert C. Intrinsic 40Hz-phase asymmetries predict tACS effects during conscious auditory perception. *PLoS One* 14: e0213996, 2019. doi:10.1371/journal.pone.0213996.

Mitra PP, Pesaran B. Analysis of dynamic brain imaging data. *Biophys J* 76: 691–708, 1999. doi:10.1016/S0006-3495(99)77236-X.

Mody M, Belliveau JW. Speech and language impairments in autism: insights from behavior and neuroimaging. *N Am J Med Sci (Boston)* 5: 157–161, 2013. doi:10.7156/v5i3p157.

Monti A, Cogiamanian F, Marceglia S, Ferrucci R, Mameli F, Mrakic-Sposta S, Vergari M, Zago S, Priori A. Improved naming after transcranial direct current stimulation in aphasia. *J Neurol Neurosurg Psychiatry* 79: 451–453, 2008. doi:10.1136/jnnp.2007.135277.

Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods* 11: 364–386, 2008. doi:10.1177/1094428106291059.

Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clin Neurophysiol* 114: 2220–2222, 2003. doi:10.1016/S1388-2457(03)00235-9.

Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 527: 633–639, 2000. doi:10.1111/j.1469-7793.2000.t01-1-00633.x.

Nobusako S, Nishi Y, Nishi Y, Shuto T, Asano D, Osumi M, Morioka S. Transcranial direct current stimulation of the temporoparietal junction and inferior frontal cortex improves imitation-inhibition and perspective-taking with no effect on the autism-spectrum quotient score. *Front Behav Neurosci* 11: 84, 2017. doi:10.3389/fnbeh.2017.00084.

Onoda K, Kawagoe T, Zheng H, Yamaguchi S. Theta band transcranial alternating current stimulations modulates network behavior of dorsal anterior cingulate cortex. *Sci Rep* 7: 3607, 2017. doi:10.1038/s41598-017-03859-7.

Oostenveld R, Fries P, Maris E, Schoffelen JM. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011: 156869, 2011. doi:10.1155/2011/156869.

Paulus W. Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods. *Neuropsychol Rehabil* 21: 602–617, 2011. doi:10.1080/09602011.2011.557292.

Picton TW, Alain C, Woods DL, John MS, Scherg M, Valdes-Sosa P, Bosch-Bayard J, Trujillo NJ. Intracerebral sources of human auditory-evoked potentials. *Audiol Neurotol* 4: 64–79, 1999. doi:10.1159/000013823.

Polanía R, Nitsche MA, Paulus W. Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Hum Brain Mapp* 32: 1236–1249, 2011a. doi:10.1002/hbm.21104.

Polanía R, Paulus W, Antal A, Nitsche MA. Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage* 54: 2287–2296, 2011b. doi:10.1016/j.neuroimage.2010.09.085.

Port RG, Anwar AR, Ku M, Carlson GC, Siegel SJ, Roberts TP. Prospective MEG biomarkers in ASD: pre-clinical evidence and clinical promise of electrophysiological signatures. *Yale J Biol Med* 88: 25–36, 2015.

Port RG, Edgar JC, Ku M, Bloy L, Murray R, Blaskey L, Levy SE, Roberts TPL. Maturation of auditory neural processes in autism spectrum disorder—A longitudinal MEG study. *Neuroimage Clin* 11: 566–577, 2016. doi:10.1016/j.nicl.2016.03.021.

Port RG, Gandal MJ, Roberts TP, Siegel SJ, Carlson GC. Convergence of circuit dysfunction in ASD: a common bridge between diverse genetic and environmental risk factors and common clinical electrophysiology. *Front Cell Neurosci* 8: 414, 2014. doi:10.3389/fncel.2014.00414.

Preisig BC, Sjerps MJ, Hervais-Adelman A, Kösem A, Hagoort P, Riecke L. Bilateral gamma/delta transcranial alternating current stimulation affects interhemispheric speech sound integration. *J Cogn Neurosci* 32: 1242–1250, 2020. doi:10.1162/jocn_a_01498.

Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, Guo M, Dawson G. Effects of a brief Early Start Denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 51: 1052–1065, 2012. doi:10.1016/j.jaac.2012.08.003.

Rojas DC, Maharajh K, Teale P, Rogers SJ. Reduced neural synchronization of gamma-band MEG oscillations in first-degree relatives of children with autism. *BMC Psychiatry* 8: 66, 2008. doi:10.1186/1471-244X-8-66.

Rojas DC, Teale PD, Maharajh K, Kronberg E, Youngpeter K, Wilson LB, Wallace A, Hepburn S. Transient and steady-state auditory gamma-band responses in first-degree relatives of people with autism spectrum disorder. *Mol Autism* 2: 11, 2011. doi:10.1186/2040-2392-2-11.

Rojas DC, Wilson LB. γ-band abnormalities as markers of autism spectrum disorders. *Biomarkers Med* 8: 353–368, 2014. doi:10.2217/bmm.14.15.

Rosenkranz K, Nitsche MA, Tergau F, Paulus W. Diminution of training-induced transient motor cortex plasticity by weak transcranial direct current stimulation in the human. *Neurosci Lett* 296: 61–63, 2000. doi:10.1016/S0304-3940(00)01621-9.

Rufener KS, Krauel K, Meyer M, Heinze HJ, Zaehle T. Transcranial electrical stimulation improves phoneme processing in developmental dyslexia. *Brain Stimul* 12: 930–937, 2019. doi:10.1016/j.brs.2019.02.007.

Rufener KS, Zaehle T, Oechslin MS, Meyer M. 40Hz-Transcranial alternating current stimulation (tACS) selectively modulates speech perception. *Int J Psychophysiol* 101: 18–24, 2016. doi:10.1016/j.ijpsycho.2016.01.002.

Schutter DJ, Hortensius R. Retinal origin of phosphenes to transcranial alternating current stimulation. *Clin Neurophysiol* 121: 1080–1084, 2010. doi:10.1016/j.clinph.2009.10.038.

Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *Neuroscientist* 17: 37–53, 2011. doi:10.1177/1073858410386614.

Stecher HI, Herrmann CS. Absence of alpha-tACS aftereffects in darkness reveals importance of taking derivations of stimulation frequency and individual alpha variability into account (vol 9, 984, 2018). *Front Psychol* 9: 984, 2018. doi:10.3389/fpsyg.2018.00984.

Steinmann S, Leicht G, Ertl M, Andreou C, Polomac N, Westerhausen R, Friederici AD, Mulert C. Conscious auditory perception related to long-range synchrony of gamma oscillations. *Neuroimage* 100: 435–443, 2014a. doi:10.1016/j.neuroimage.2014.06.012.

Steinmann S, Leicht G, Mulert C. Interhemispheric auditory connectivity: structure and function related to auditory verbal hallucinations. *Front Hum Neurosci* 8: 55, 2014b. doi:10.3389/fnhum.2014.00055.

Sun L, Grützner C, Bölte S, Wibral M, Tozman T, Schlitt S, Poustka F, Singer W, Freitag CM, Uhlhaas PJ. Impaired gamma-band activity during perceptual organization in adults with autism spectrum disorders: evidence for dysfunctional network activity in frontal-posterior cortices. *J Neurosci* 32: 9563–9573, 2012. doi:10.1523/JNEUROSCI.1073-12.2012.

Suzuki K, Fujiwara T, Tanaka N, Tsuji T, Masakado Y, Hase K, Kimura A, Liu M. Comparison of the after-effects of transcranial direct current stimulation over the motor cortex in patients with stroke and healthy volunteers. *Int J Neurosci* 122: 675–681, 2012. doi:10.3109/00207454.2012.707715.

Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J Neurosci* 16: 4240–4249, 1996. doi:10.1523/JNEUROSCI.16-13-04240.1996.

Tierney AL, Gabard-Durnam L, Vogel-Farley V, Tager-Flusberg H, Nelson CA. Developmental trajectories of resting EEG power: an endophenotype of autism spectrum disorder. *PLoS One* 7: e39127, 2012. doi:10.1371/journal.pone.0039127.

Tort AB, Komorowski R, Eichenbaum H, Kopell N. Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *J Neurophysiol* 104: 1195–1210, 2010. doi:10.1152/jn.00106.2010.

van den Heuvel MP, Sporns O. A cross-disorder connectome landscape of brain dysconnectivity. *Nat Rev Neurosci* 20: 435–446, 2019. doi:10.1038/s41583-019-0177-6.

Van Hecke AV, Stevens S, Carson AM, Karst JS, Dolan B, Schohl K, McKindles RJ, Remmel R, Brockman S. Measuring the plasticity of social approach: a randomized controlled trial of the effects of the PEERS intervention on EEG asymmetry in adolescents with autism spectrum disorders. *J Autism Dev Disord* 45: 316–335, 2015. doi:10.1007/s10803-013-1883-y.

van Steenburgh JJ, Varvaris M, Schretlen DJ, Vannorsdall TD, Gordon B. Balanced bifrontal transcranial direct current stimulation enhances working memory in adults with high-functioning autism: a sham-controlled crossover study. *Mol Autism* 8: 40, 2017. doi:10.1186/s13229-017-0152-x.

Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biol Psychiatry* 77: 1089–1097, 2015. doi:10.1016/j.biopsych.2015.04.016.

Wilson JE, Quinn DK, Wilson JK, Garcia CM, Tesche CD. Transcranial direct current stimulation to the right temporoparietal junction for social functioning in autism spectrum disorder: case report. *J ECT* 34: e10–e13, 2017. doi:10.1097/YCT.0000000000000445.

Wilson TW, Rojas DC, Reite ML, Teale PD, Rogers SJ. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biol Psychiatry* 62: 192–197, 2007. doi:10.1016/j.biopsych.2006.07.002.

Wöstmann M, Herrmann B, Maess B, Obleser J. Spatiotemporal dynamics of auditory attention synchronize with speech. *Proc Natl Acad Sci USA* 113: 3873–3878, 2016. doi:10.1073/pnas.1523357113.

Wöstmann M, Vosskuhl J, Obleser J, Herrmann CS. Opposite effects of lateralised transcranial alpha versus gamma stimulation on auditory spatial attention. *Brain Stimul* 11: 752–758, 2018. doi:10.1016/j.brs.2018.04.006.